Friday
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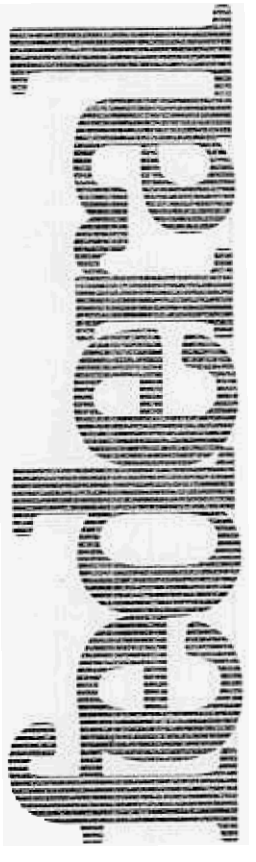
Part II



Department of Health and Human Services

Food and Drug Administration

21 CFR Part 610

Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. 80N-0208]

Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations in response to the report and recommendations of the Panel on Review of Bacterial Vaccines and Toxoids (the Panel). The Panel reviewed the safety, efficacy, and labeling of bacterial vaccines and toxoids with standards of potency, antitoxins, and immune globulins. On the basis of the Panel's findings and recommendations, FDA is proposing to classify these products in Category I (safe, effective, and not misbranded), Category II (unsafe, ineffective, or misbranded), or Category IIIB (off the market pending completion of studies permitting a determination of effectiveness). Products recommended for Category IIIA (formerly defined as on the market during further studies in support of effectiveness) will be reviewed by the Vaccines and Related Biological Products Advisory Committee for reclassification into Category I or II. In the near future, FDA will publish a notice of opportunity for hearing (NOH) to revoke the licenses for products in Category II and Category IIIB. Comments and additional data will be requested in the NOH.

DATES: Comments on the proposed classification of products into Category I and on proposed amendments to the biologics regulations should be submitted by March 13, 1986. Comments on the confidentiality of data submitted for review by the Panel should be submitted before January 13, 1986. FDA proposes that any final regulation based on this proposal become effective 60 days after the date the final regulation is published in the **Federal Register.** Labeling requirements, including the requirements in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57), would become effective 30 months after the date of publication of the final rule in the **Federal Register.**

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Steven F. Falter, Center for Drugs and Biologics (HFN-364), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of February 13, 1973 (38 FR 4319), FDA issued § 601.25 (21 CFR 601.25) concerning procedures for the review of the safety, effectiveness, and labeling of biological products licensed prior to July 1, 1972. Under the panel assignments published in the **Federal Register** of June 19, 1974 (39 FR 21176), the biological products reviewed were assigned to one of the following categories: (a) Bacterial vaccines and bacterial antigens with "no U.S. standard of potency," (b) bacterial vaccines and toxoids with standards of potency, (c) viral vaccines and rickettsial vaccines, (d) allergenic extracts, (e) skin test antigens, and (f) blood and blood derivatives.

Under § 601.25, FDA assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory panel consisting of qualified experts to ensure objectivity of the review and public confidence in the use of these products. Each panel was charged with preparing an advisory report to the Commissioner which was to: (1) Evaluate the safety and effectiveness of the biological products, (2) review labeling of the biological products, and (3) identify the biological products under review that are safe, effective, and not misbranded. The advisory report includes recommendations classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. The Panel's statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by the Panel to be unsafe, ineffective, or misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. Those biological products in Category III for which continued licensing, manufacturing, and marketing during the period of further testing are recommended are designated as Category IIIA. Those biological products in Category III for which suspension of the product licenses pending submission of additional data are recommended are designated as Category IIIB. The recommendation for either Category IIIA or IIIB is based on assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time, while questions raised concerning the products are being resolved by further study.

The definition above of Category IIIA was applied at the time of the Panel's review and served as a basis for the Panel's recommendations. In the **Federal Register** of October 5, 1982 (47 FR 44062), FDA revised § 601.25 and created a new § 601.26 (21 CFR 601.26) to provide for the review by an advisory review panel of products currently recommended to be in Category IIIA. The purpose of the review will be to reclassify each Category IIIA product into either Category I or Category II as defined above, based on the available evidence for effectiveness. A more detailed description of the procedures for the review and reclassification of the products recommended for Category IIIA by the Panel appears later in this document in paragraph 1d of FDA's response to the Panel's report.

In this advisory report, some biological products are designated as Category IIIC, based on the Panel's conclusion that it was not possible to classify these products because of essentially administrative problems, rather than because of scientific questions. For example, some licenses are held for products which the manufacturer has not produced or marketed for many years. Other licenses are held for products for which there is no labeling, and which are manufactured only for combination with other biologically active components. The Panel has recommended that the licenses for products placed in Category IIIC be revoked, because the Panel was unable to determine the potential benefits and risks of the products in the event they were to be marketed. However, the Panel noted that in some cases it may be preferable for FDA and the manufacturer to take appropriate administrative actions to satisfactorily resolve information deficiencies, rather than to revoke the product license.

In the **Federal Register** of February 28, 1973 (38 FR 4359), FDA requested data and information regarding bacterial vaccines and toxoids with U.S.

standards of potency. Additional data and information regarding the safety and effectiveness of related immune globulins and sera were requested in the Federal Register of June 19, 1974 (38 FR 21176).

Some concern has been expressed that information submitted to FDA under § 601.25 will become public information. Data and information submitted in response to the February 28, 1973 and June 19, 1974 notices and falling within the provisions of 5 U.S.C. 552(b), 18 U.S.C. 1905, or 21 U.S.C. 331(j) have been handled as confidential. However, with the publication of this proposed implementation and the Panel's findings, such data and information will, under § 601.25(b)(2), be made publicly available after January 13, 1986, and may be reviewed at the office of the Dockets Management Branch, except to the extent that the person submitting the data and information demonstrates that it still falls within the confidentiality provisions of one or more of the above statutes. Accordingly, comments concerning confidentiality should be submitted by January 13, 1986. A letter dated October 21, 1985, was sent to each manufacturer having products under review by this Panel, informing them of the impending release of data and information and asking that the manufacturers promptly submit any comments concerning confidentiality.

The Panel appointed by FDA to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of bacterial vaccines, toxoids, related antitoxins, and immune globulins included the following individuals:

Panel Chairman, Gene H. Stollerman, M.D., Professor and Chairman, Department of Medicine, University of Tennessee College Memphis, TN 38163 (now Professor of Medicine, Boston University Medical Center);

Geoffery Edsall, M.D. (deceased), Professor Emeritus of Microbiology (Harvard School of Public Health and London School of Hygiene and Tropical Medicine);

Theodore C. Eickhoff, M.D., Professor of Medicine, Head, Division of Infectious Diseases, University of Colorado Medical Center, Denver, CO 80262;

John C. Feeley, Ph.D., Chief, Bacterial Immunology Branch (now Assistant Director for Laboratory Sciences, Bacterial Disease Division), Centers for Disease Control, Atlanta, GA 30333;

Hjordis M. Foy, M.D., Ph.D. Associate Professor (Since July 1, 1976, Professor), Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195;

Edward A. Mortimer, Jr., M.D., Chairman of the Department of Pediatrics, School of Medicine, University of New Mexico, Albuquerque, NM 87131. (Since February 1, 1975, Professor and Chairman of the Department of Community Health and Professor of Pediatrics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106.)

Jay P. Sanford, M.D., Professor, Department of Internal Medicine, University of Texas, Southwestern Medical School at Dallas, Dallas, TX 75235. (Since June 1, 1975, Dean, School of Medicine, Uniformed Services University, Bethesda, MD 20014.)

The Panel was convened on July 12, 1973, in an organizational meeting. Working meetings were held on: July 12, September 24–25, November 9–10, December 13–14, 1973; February 13–14, April 9–10, June 13–14, September 12–13, November 7–8, 1974; January 13–14, February 24–25, May 15–16, June 19–20, September 11–12, November 20–21, 1975; January 12–13, March 27–28, May 17–18, July 22–23, October 23, December 14–15, 1976; March 24–25, December 12–13, 1977; and February 1–2, 1979.

Two nonvoting liaison representatives served on the Panel. Ms. Laryl Lee Delker, nominated by the Consumer Federation of America, served as the consumer representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D., substituted for Dr. Adams during his absences. Morris Schaeffer, M.D., Ph.D., participated in the Panel meetings in his capacity as Director of the Office of Scientific Advisors and Consultants, FDA. Jack Gertzog, Deputy Director, Office of Scientific Advisors and Consultants, FDA, served as Executive Secretary of the Panel. Margaret Pittman, Ph.D., was selected by the Panel as a consultant.

Over 120 persons requested an opportunity or were otherwise invited to appear before the Panel and present their views on one or more of the vaccines and related matters. Every person who requested an opportunity was heard by the Panel. The names of these persons are on file with the Dockets Management Branch.

The Panel on Review of Bacterial Vaccines and Toxoids evaluated all data submitted for the following vaccines, toxoids, and other related products:

TABLE 1.—LIST OF PRODUCTS REVIEWED BY PANEL

Manufacturer	Product
Abbott Laboratories.....	Tetanus immune globulin (human).
Advance Biofacturers Corp.	Collagenase.
Armour Pharmaceutical Co.	Tetanus immune globulin (human).
Bureau of Laboratories, Michigan Department of Public Health.	Anthrax vaccine adsorbed, diphtheria antitoxin, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, diphtheria toxoid adsorbed, pertussis vaccine, pertussis vaccine adsorbed, tetanus immune globulin (human), tetanus toxoid adsorbed, typhoid vaccine.
Connaught Laboratories, Ltd.	BCG vaccine, botulism antitoxin, diphtheria toxoid, tetanus toxoid.
Cutter Laboratories, Inc.	Pertussis immune globulin (human), plaque vaccine, tetanus immune glob-ulin (human), tetanus toxoid.
Dow Chemical Co. (The)	Diphtheria and tetanus toxoids adsorbed, diphtheria tetanus toxoids and pertussis vaccine adsorbed, diphtheria toxoid, diphtheria toxoid and pertussis vaccine adsorbed, pertussis vaccine, tetanus immune glob-ulin (human), tetanus toxoid tetanus toxoid, adsorbed.
Eli Lilly and Co.....	Cholera vaccine, diphtheria and tetanus toxoids, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, pertussis vaccine, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, tetanus toxoid adsorbed, typhoid vaccine.
E.R. Squibb and Sons, Inc.	Tetanus immune globulin (human).
Glaxo Laboratories, Ltd	BCG vaccine.
Istituto Sieroterapico Vaccinogeno Toscano "Sclavo".	Diphtheria antitoxin, diphtheria toxoid, diphtheria toxoid adsorbed, tetanus antitoxin, tetanus toxoid, tetanus toxoid adsorbed.

TABLE 1.—LIST OF PRODUCTS REVIEWED BY PANEL—Continued

Manufacturer	Product
Lederle Laboratories, Division of American Cyanamid Co.	lotulism antitoxin, cholera vaccine, diphtheria antitoxin, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, gas gangrene polyvalent antitoxin, pertussis vaccine, streptokinase-streptodornase, tetanus antitoxin, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus and gas gangrene polyvalent antitoxin, tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed.
Massachusetts Public Health Biologic Laboratories	iphtheria antitoxin, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, diphtheria toxoid, tetanus antitoxin, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed, typhoid vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	holera vaccine, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, tetanus toxoid adsorbed, tetanus immune globulin (human), typhoid vaccine.
Merrell-National Laboratories, Division of Richardson-Merrell, Inc.	holera vaccine, diphtheria antitoxin, diphtheria and tetanus toxoids and Pertussis vaccine, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, Pertussis vaccine, tetanus antitoxin, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, tetanus toxoid adsorbed.
Metabolic, Inc	tanus immune globulin (human).
Osterreichisches Institut Fur Haemoderivate G.m.b.H.	tanus immune globulin (human).
Parke, Davis and Co	phtheria and tetanus toxoids, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed and poliomyelitis vaccine, diphtheria and tetanus toxoids and pertussis and poliomyelitis vaccine adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, diphtheria toxoid adsorbed, Pertussis vaccine, Pertussis vaccine adsorbed, tetanus antitoxin, tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed.
Swiss Serum and Vaccine Institute, Berne.	tanus antitoxin, tetanus toxoid adsorbed.
Texas Department of Health Resources.	phtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, Pertussis vaccine, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, typhoid vaccine.
Travenol Laboratories, Inc., Hyland Division.	rtussis immune globulin (human), tetanus immune globulin (human).
University of Illinois	CG vaccine.

TABLE 1.—LIST OF PRODUCTS REVIEWED BY PANEL—Continued

Manufacturer	Product
Wyeth Laboratories, Inc.	Cholera vaccine, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, diphtheria toxoid adsorbed, Pertussis vaccine, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed, typhoid vaccine.

Only biological products that were licensed prior to July 1, 1972, are reviewed in this report.

The Advisory Panel appointed to review data and information concerning safety, effectiveness, and labeling of bacterial vaccines and toxoids has completed its review as follows:

Basis of Evaluation

1. *General background and history.* The diseases of man caused by bacteria and by some of their specific extracellular toxins from which useful vaccines have been produced represent extraordinarily diverse pathologic processes. The diseases range from tetanus to tuberculosis; the former is an accute illness caused by a single well-defined toxin and the letter is a chronic disease due to intricate bacterial-host cell interactions resulting in a wide variety of lesions. Moreover, the degree of protection offered by current immunization practices against these diseases range from virtually complete efficacy, as in the case of tetanus, to a very limited and temporary benefit, as in the case of choloera. A brief account of the history of immunization against these diseases may help both the lay and professional public to appreciate the background of our current achievements and dilemmas against which this Panel has been obliged to exercise its judgment in assesing the safety and efficacy of the products under its purview.

It is important for the public and its agencies to appreciate the tentative and envolving nature of the science of immuization, particulary to combat the notion that decisions made in the public interest at one point in time are necessarily valid and binding at another. The foundations of the modern science of bacteriology are more than a century old and were laid by Louis Pasteur and Robert Koch, who died within the momory of some persons still alive. Pasteur not only established the germ theory of disease, but, just 100 years ago (in 1877) discovered and applied the principles of active immunization by using living, attenuated cultures—"live vaccines." He argued that if Jenner could use cowpox (what Pasteur thought to be attenuated smallpox) as a vaccine, the same might be done with attenuated anthrax. This he succeeded in doing in preparing attenuated chicken cholera and anthrax vaccines for animals. Subsequently, "killed' bacterial vaccines were made by the end of the 19th century when A. E. Wright in England, among others, began immunizing against typhoid fever with heat-killed whole bacterial cells. Epidemics of cholera and plague, rampant in various parts of the world at the time, were quickly attacked with other vaccines many of which were similarly made from killed whole bacteria. In all three diseases, the vaccines seemed to afford some useful protection before advances could be made in worldwide sanitation and well before the instruction of antibiotics.

At the close of the 19th century, Koch was attempting to prevent and even to treat tuberculosis with tuberculin, the culture filtrate of tuburcule with bacilli. His failure to do so, plus the serious toxic and untoward effects that this treatment had on the disease, created reservations in the minds of both professionals and the public concerning the risks as well as the benefits of immunization attempts. Nonetheless, despite this setback, the first living bacterial vaccine to be used on a large scale in man came as a sequel to Koch's work when Calmette and Guerin introduced BCG vaccine into human immunization procedures in 1921.

To appreciate the speed of the development of the science of immunology, it is necessary to acknowledge not only the dramatic empirical discoveries of successful vaccines, but also the discovery of the immunologic processes upon which further progress in immunization was based. Two major forms of host defenses are referred to repeatedly in this report. They also have their origins in the medically tumultuous era of the late 19th century. Eli Metchnikoff, the Russion biologist who studied under Pasteur and eventually become a director of the Pasteur Institute, developed the concept of "phagocytosis." He gave the name of "phagocytes" (eating cells) to body cells in blood, blood vessels, lymph nodes, bone marrow, liver, and spleen which digest and destroy invading microorganisms as well as other foreign microparticles. This system of cellular immunity, responsible for the clearing of foreign agents from within the host, he considered to be the backbone of host

defense against infection. The "humoral theory" was introduced at the same time by G. H. F. Nutthall of Cambridge who studied the killing action of blood on bacteria (bactericidal effects). He showed these effects were due to chemical products of cells in blood serum and body fluids—substances called "antibodies" which could destroy or inactive some bacteria without help from phagocytes. By 1894, Richard Pfeiffer, one of Koch's pupils, demonstrated that such antibodies caused the disintegration of cholera vibrios. These he called "bacteriolysins."

The synthesis of humoral and cellular mechanisms of immunity was proposed by the Wright in 1903 when he demonstrated the prophagocytic effect of specific antibodies. Wright named antibodies "opsonins" or "bacteriotropins" which enhance the ability of phagocytic cells to recognize, ingest, and kill microorganisms. Although Wright's concepts of the interaction of antibodies and and cells applied well to antibacterial immunity against invasive bacterial diseases such as typhoid, pneumonia, streptococcal infections, and meningitis, it did not pertain as much to diseases produced by the action of toxins liberated by bacteria.

In diseases like diphtheria, tetanus, and botulism, neutralization of the soluble bacterial toxins (exotoxins) liberated during infection is of the utmost importance in the prevention of the diseases caused by these organisms. Thus, antibodies that neutralize such toxins are the basis of "antitoxic immunity," which constitutes an area of immunologic knowledge that is on a much firmer basis than the understanding of many forms of antibacterial immunity.

Again, in the last two decades of the 19th century, the principles of antitoxic immunity were established when Pasteur's associate, Pierre Roux, showed the dephtheria bacillus produced a powerful soluble toxin in the culture filtrate of the organism. Behring and Kitasato, disciples of Koch, by 1890 had prepared an antibody to the diphtheria toxin which they termed "antitoxin" and with such immune sera began the era of "passive immunization." Thus, antitoxin (serum prepared in horses against such toxins) could be used to prevent and treat certain diseases. The denaturation of the toxins with the addition of formalin rendered them harmless when injected into man and animals, but they still retained their ability to produce antitoxin antibodies. "Active" immunization against diphtheria and tetanus with these toxoids subsequently became routine in most countries of the world.

"Passive" immunization consists of the injection of antibodies made by another host, human or animal, into the person to be protected. Antibodies remain in that person for only a short time, however, until they are broken down, and thus provide only temporary benefit. Active immunization, on the other hand, consists of inducing the person to be protected to produce their own antibodies by giving small doses of the microorganism or toxin in a form that will not cause serious illness in the person. Once active immunity is induced, it tends to persist for long periods of time.

The important differences between passive and active immunization were clearly established in the 1890's by Jules Bordet and by Paul Ehrlich whose brilliant career not only included the standardization of toxins and antitoxins and the foundations of modern immunochemistry, but also led to the recognition of the presence in the blood and body tissues of "complement," the system of enzymes that are activated by antigen-antibody complexes and that result in the cellular and vascular events of inflammation leading to the destruction of bacteria and viruses and to the stimulation of the host cells which phagocytize and destroy organisms.

From Ehrlich's systematic, quantitative approach to the neutralization of toxins emerged the triumph over diphtheria and subsequently, even more brilliantly, over tetanus. By the First World War, the lives of many wounded men were saved by passive tetanus immunization and the control of tetanus during the Second World War with the toxiod could be regarded as a modern miracle of immunization.

Soon after the beginnings of immunology came the development of government supervising authorities in many countries to regulate standards of purity and potency to which preparations had to conform before they were released for public usage. The importance of international standards of vaccines was recognized by the Health Commission of the League of Nations which in 1929 appointed a permanent Commission on Biological Standardization. As a result, potency of vaccines were expressed in a more uniform notation which was accepted and understood throughout the world.

In the United States and Great Britain, the control of biological substances for sale became essentially the responsibility of the producing laboratory, but manufacturers worked under licenses issued by government agencies such as the current Bureau of Biologics, Food and Drug **Administration, and Great Britain's Ministry of Health, respectively, and under standards of safety and potency** defined by the regulations developed by these agencies. (Note: Because of a reorganization of FDA accomplished after the Panel submitted its report, the Bureau of Biologics is now the Office of Biologics Research and Review, Center for Drugs and Biologics (see 49 FR 10166; March 19, 1984).)

It has become generally understood that a successful and acceptable vaccine must be: (1) Safe and (2) effective. Safety means that the preparation used must not cause the disease against which it is directed and that the occurrence of reactions, both local and general, must be within acceptable limits. Efficacy implies a useful degree of clinical protection: In some infections, the best guide to immunity is the amount of circulating antibody in the blood against the causative agent. It is the **clinical trial, however, which must** provide the final critical assessment of the efficacy and safety of the new vaccine. The basic requirements of filed trials meeting modern critical criteria were well described by 1957 by W.C. Cockburn, and are elaborated upon in the Panel's generic statement on the requirements for a well-controlled field trial.

The World Health Organization, which was established in 1948, encouraged international cooperation in solving health problems and has been helpful in continuing with the work on establishing and promoting international standards for biological products which had begun with the work of the League of Nations.

The growing sophistication of the standardization of vaccines ultimately resulted in changes in Federal law and regulations whereby this Panel was established to help to determine whether currently licensed vaccines produced according to specified standards of potency are both safe and effective for human usage. Although the aims of the act are praiseworthy and the action timely, the judgment concerning safety and efficacy of bacterial vaccines and toxoids presents some complex and knotty overall problems.

2. *Overall problems*—a. *Determination of safety*—(1) *Risk/benefit assessment.* The concept of risks and benefits is a fundamental one in a consideration of vaccines, or any other therapeutic or preventive modality. Risks are considered to include the risk